REMARKS

Applicants thank the Examiner for the helpful telephone interview with the undersigned on March 3, 2003.

Claims 1-4, 6, 8, 9-13, and 36-80 are pending in the application, claims 5, 7, and 14-35 having been cancelled and claims 36-80 having been added by the above amendment. Claims 1, 2, and 4 have been amended. Support for the amendments and new claims can be found in original claims 1-13 and in the specification at, e.g., page 2, line 2, to page 3, line 12; and page 20, lines 9-19. No new matter has been added.

The Invention

The present invention is based, at least in part, on Applicants' discovery that a fusion protein containing an Hsp60 protein and an HPV type 16 antigen was effective in treating warts caused by HPV types other than type 16. In light of this novel finding, the present claims cover a method of treating a wart by administering a fusion protein containing a protein antigen from HPV. Moreover, the claims specify that the type of HPV that causes the wart is different from the type of HPV administered to the subject.

35 U.S.C. § 112, 2nd Paragraph (Indefiniteness)

On pages 2-3 of the Office Action, the Examiner rejected claims 1-13 as allegedly indefinite. The several indefiniteness rejections are addressed in the order that they appear in the Office Action. While certain claim terms have been amended, this is not an admission that any of the original claim terms were unclear.

Claim 1 has been amended to remove the phrase "suspected of having a wart." Thus, the Examiner's rejection in view of this phrase is moot.

The Examiner objected to the following phrases: "heat shock protein;" "immunostimulatory fragment;" "HPV protein;" and "antigenic fragment."

Claim 1 now recites "Hsp60," instead of a "heat shock protein" and "HPV E7," in place of "HPV." One of ordinary skill in the art would know whether a given protein is an Hsp60 protein or an HPV E7 protein. In view of the specification of the amended terms, this ground for rejection should be withdrawn. With respect to the other two terms, the specification makes it clear that an "immunostimulatory fragment" of an Hsp60 protein is a portion of the Hsp60 protein that, when administered to a subject, facilitates an immune response to the HPV E7 protein or antigenic fragment thereof (see specification at page 4, line 29, to page 5, line 6). An "antigenic fragment" of an HPV E7 protein is a portion of the HPV E7 protein that, when administered to a subject, elicits an immune response against the HPV E7 protein or the HPV E7 protein fragment (see specification at page 4, lines 18-28).

The claimed methods encompass the use of a fusion protein that contains fragments, but those fragments must have the functional properties recited in the claims (*i.e.*, they must be immunostimulatory or antigenic). Because a person of ordinary skill in the biological arts would readily understand the meaning and scope of these claim terms, the metes and bounds of the claims are clear. Accordingly, the claims as amended satisfy the definiteness requirement.

The Examiner asserted that the phrase "amount sufficient" renders claim 1 indefinite. The claim requires that the recited composition be administered to a subject "in an amount sufficient to treat the wart." It is well known in the art that the amount of a composition administered to a given subject may vary based upon factors such as the subject's sex, weight, age, or the severity of their disease. Because a person of ordinary skill in the biological arts understands that the "amount sufficient" to treat a wart may vary from subject to subject, and would be able to recognize whether or not a given dosage was sufficient to treat a wart, the claim term is sufficiently definite. Accordingly, applicants request that the Examiner withdraw the rejection.

The Examiner rejected claim 1 as allegedly incomplete for omitting essential steps. According to the Examiner, the omitted "steps" are "the hsp protein type which would be suited to treat HPV, the HPV protein, the 'fragment, the amount."

Amended claim 1 recites both the hsp (Hsp60) and HPV protein (HPV E7) used in the claimed method. As detailed herein, the terms "immunostimulatory fragment," "antigenic fragment," and "amount sufficient" have well-defined meanings to the skilled artisan that clearly establish the metes and bounds of the claimed method. Furthermore, the "administering" step of claim 1 is clear, and the Examiner does not appear to have suggested that any essential step is missing from the claimed method. Rather, the Examiner's comments are directed to features of the fusion protein that is administered in the claimed method. For the reasons presented herein, all of the claim terms have clear meanings that are well understood by a person of ordinary skill in the biological arts. Accordingly, the claimed method does not omit essential matter and applicants request that the Examiner withdraw the rejection.

35 U.S.C. § 112, 1st Paragraph (Enablement)

On pages 3-5 of the Office Action, the Examiner rejected claims 1-13 as allegedly not enabled. According to the Examiner (emphasis added):

> ...the specification, while being enabling for a method of inducing [an] immune response utilizing Hsp65 heat shock proteins complexed with E7 protein of human papillomavirus (HPV) does not reasonably provide enablement for method of *any and all* types of epitopes of *any and all* human papillomavirus proteins whether it be early or late proteins complexed with *any and all* heat shock proteins to induce an immune response absent inducing [a] severe adverse effect. Nor [does] the specification set (*sic.*) any disclosure for teaching of *any and all* fusion proteins of HPV proteins and immunostimulatory fragments. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use *the invention commensurate in scope with these claims.* The specification does not set forth an adequate teaching *for the broad scope* of the claimed invention, in order to enable *the full scope* of the method one need products that would actually enable the process. ... The claims currently *are broadly reciting any epitope from HPV* ... The results from E7 cannot be extrapolated to *any and all* early papillomavirus proteins. ... the specification does not teach or provide any guidance for development *of a broad complex of all epitopes and all heat shock proteins* ...

In view of the present amendment, Applicants ask that the Examiner reconsider and withdraw this ground for rejection.

The Examiner has found that a method that encompass administering a fusion protein containing an Hsp65 protein and an HPV E7 protein is enabled, and Applicants' claims now

recite "HPV E7" and "Hsp60," Hsp60 being a family of proteins that includes Hsp65 (specification at page 7, lines 26-29, and page 8, lines 24-27 describing hsp families such as Hsp60, Hsp70, and Hsp90). Accordingly, applicants have used the term "Hsp60 protein" to properly describe the family to which mycobacterial Hsp65 belongs.

In addition, the claimed methods encompass administration of a fusion protein that contains an immunostimulatory *fragment* of an Hsp60 protein and/or an antigenic *fragment* of an HPV E7 protein.

Fusion proteins containing fragments having the functional properties recited in the claims can, like fusion proteins containing full-length HPV E7 and/or Hsp60 proteins, be easily made by the skilled biologist. Recombinant techniques, which are one of the ways fusion proteins can be produced, are carried out routinely. Moreover, fusion proteins containing a fragment of a protein can be administered in the same way as a fusion protein containing only full-length proteins. Given the level of skill in the art and the breadth of the present claims, this ground for rejection should now be withdrawn.

35 U.S.C. § 112, 1st Paragraph (Written Description)

On pages 6-8 of the Office Action, the Examiner rejected claims 1-13 as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. According to the Examiner, "applicants have not disclosed a method of inducing immune response with any and all heat shock proteins or immunostimulatory fragments."

Amended claim 1 is directed to a method of treating a wart in a subject by administering to the subject a fusion protein containing an Hsp60 protein (or an immunostimulatory fragment thereof) and an HPV E7 protein (or an antigenic fragment thereof). As detailed herein, an "immunostimulatory fragment" of an Hsp60 protein is a portion of the Hsp60 protein that, when administered to a subject in accordance with the claimed method, facilitates an immune response to the HPV E7 protein or antigenic fragment thereof (see specification at page 4, line 29, to page 5, line 6). A skilled artisan, at the time the present application was filed, would have

understood applicants to have been in possession of a fusion protein containing an Hsp60 protein or an immunostimulatory fragment thereof.

The Examiner has cited *Regents of the University of California v. Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997), a leading case on the written description requirement for nucleic acid molecules, in support of the present rejection. The discussion in *Lilly* regarding a proper written description for genus claims had to do with a claim drawn to a vertebrate mRNA encoding insulin. The *Lilly* court held that a generic statement, such as the term "mammalian insulin cDNA" is not, without more, an adequate written description of an invention claiming the nucleotide sequence for human insulin. The court's decision in *Lilly* focused on functional claims directed merely to a desired result without structure. However, the *Lilly* court also took care to indicate that structural information about the claimed genus was different in kind than a mere desired result. The court indicated that in claims involving chemical materials such as proteins and polynucleotides "generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is usually an adequate description of the claimed genus." *Id.*

An immunostimulatory fragment of an Hsp60 is limited both by structure (a portion of an Hsp60 protein) as well as function (it must have an "immunostimulatory" activity, as that term is described herein). The fusion protein recited in the claimed methods claims is not described in terms of a desired result without structure, as was the case in *Lilly*. Furthermore, the fusion protein recited in the claimed methods encompasses Hsp60 proteins (and fragments thereof) having amino acid sequence that were known in the art at the time of filing the present application. This contrasts with *Lilly* where the claimed subject matter was a nucleic acid sequence (composition) that had not been described in the prior art.

In light of the above, a person of ordinary skill in the art would clearly understand the structural/functional definition of the fusion protein recited in the claims and would therefore understand applicants to have been in possession of the claimed subject matter at the time the application was filed. Accordingly, applicants submit that the claims as amended satisfy the written description requirement and request that the Examiner withdraw the rejection.

35 U.S.C. § 102(b)

On pages 8-9 of the Office Action, the Examiner rejected claims 1-3 and 5-13 as allegedly anticipated by Mizzen et al., WO 99/07860 ("Mizzen"). According to the Examiner, Mizzen "taught the composition of heat shock proteins fused to E7 proteins of human papillomavirus and method of utilizing the said proteins in treating and inducing immune response."

As noted above, amended claim 1 covers a method of treating a wart in a subject by administering a fusion protein containing an Hsp60 protein (or an immunostimulatory fragment thereof) and an HPV E7 protein (or an antigenic fragment thereof). The claim also specifies that the wart is caused by an infection with an HPV type that differs from the HPV antigen contained in the fusion protein.

Mizzen's disclosure does not anticipate independent claim 1. For a prior art reference to anticipate a claimed invention, that reference must disclose exactly what is claimed. Each and every element of the claimed invention must be disclosed in enabling detail. *See Scripps Clinic & Res. Found. v. Genentech, Inc.*, 927 F.2d 1565 (Fed. Cir. 1991). Here, Mizzen does not anticipate the present claimed method because Mizzen does not describe using a fusion protein containing an HPV protein antigen of one HPV type to treat a wart caused by an infection with a second HPV type. Accordingly, Mizzen cannot anticipate the claimed invention, and this ground for rejection should be withdrawn.

On page 9 of the Office Action, the Examiner rejected claims 1-4 and 6-13 as allegedly anticipated by Chu et al. (1998) FASEB J. 12(5):A909 ("Chu"). According to the Examiner, Chu "taught the fusion of Hsp65 and E7 protein of human papillomavirus would induce therapeutic effect."

Chu does not describe using a fusion protein containing an HPV protein antigen of one HPV type to treat a wart caused by an infection with a second HPV type. Because Chu does not disclose each and every element of independent claim 1, Chu does not anticipate the claimed invention. Applicants request that the Examiner withdraw the rejection.

On page 9 of the Office Action, the Examiner rejected claims 1 and 8-13 as allegedly anticipated by Whittle et al., WO 98/04706 ("Whittle"). According to the Examiner, Whittle "taught the fusion papillomaviruses combined with immunostimulatory molecules."

Whittle does not disclose a fusion protein containing an Hsp60 protein (or an immunostimulatory fragment thereof) and an HPV E7 protein (or an antigenic fragment thereof), much less the use of an Hsp60-HPV E7 fusion protein to treat a wart in a subject. Because Whittle does not describe the fusion protein recited in claim 1 and the claims that depend therefrom, Whittle does not anticipate the claimed invention. Applicants request that the Examiner withdraw the rejection.

35 U.S.C. § 102(a)

On pages 10-11 of the Office Action, the Examiner rejected claims 1-4 and 6-13 as allegedly anticipated by Zhou, CN1248631A. According to the Examiner, "[t]he disclosure and claims of the above cited Chinese patent meets the claimed invention (see the entire abstract, and claims 1, 4)." The Examiner also stated that "[t]he patent is in Chinese, the examiner has utilized the resources available to the patent Office by obtaining a standby translation of the said patent, and has come to the conclusion that Zhou's patent indeed anticipates the now claimed invention."

As detailed herein, amended claim 1 is directed to a method of treating a wart in a subject by administering to the subject a fusion protein containing an Hsp60 protein (or an immunostimulatory fragment thereof) and an HPV E7 protein (or an antigenic fragment thereof), wherein the wart is caused by an infection with an HPV type that differs from the HPV type of the E7 protein (or an antigenic fragment thereof) contained in the fusion protein.

Zhou does not describe treating a wart by administering to a subject a fusion protein containing an HPV protein antigen of one HPV type to treat a wart caused by an infection with a second HPV type. Because Zhou does not disclose every element of independent claim 1, Zhou cannot anticipate the claimed invention. Accordingly, Applicants request that the Examiner withdraw the rejection.

On page 11 of the Office Action, the Examiner rejected claims 1-3 and 5-13 as allegedly anticipated by Chen et al. (2000) Cancer Res. 60:1035-42 ("Chen"). According to the Examiner,

> Chen et al taught a fusion of heat shock protein of Hsp70, and papillomavirus E7 protein genes can be utilized in treating human papillomavirus (see the abstract). Applicants are reminded that upon administration of the fusion genes the translated proteins at the cellular milieu are responsible for induction of immune response and not the genes. Hence the product and method of utilizing the product inherently do what the applicants invention is intent to accomplish. The burden is on the applicant to show that such is not case.

Chen describes a nucleic acid vaccine and the administration of the vaccine to an animal via a helium-driven gene gun apparatus. Contrary to the Examiner's comments reproduced above, administering a nucleic acid to a subject is not the same as administering a fusion protein to a subject. A nucleic acid may result in the production of a given protein within a cell of the subject, but only after administration of the nucleic acid. Because Chen describes the administration of a nucleic acid vaccine to an animal, and not a fusion protein as is required by claim 1, Chen does not anticipate the claimed method. Furthermore, Chen does not describe using a fusion protein containing an HPV protein antigen of one HPV type to treat a wart caused by an infection with a second HPV type. In light of these comments, Applicants request that the Examiner withdraw the rejection.

On pages 11-12 of the Office Action, the Examiner rejected claims 1-3 and 5-13 as allegedly anticipated by Liu et al. (2000) J. Virol. 74(6):2888-94 ("Liu"). According to the Examiner,

> Li et al taught a fusion of heat shock protein of Hsp70, and papillomavirus E7 protein genes can be utilized in treating human papillomavirus (see page 2889, left column, 1st full paragraph). Applicants are reminded that upon administration of the fusion genes the translated proteins at the cellular milieu are responsible for induction of immune response and not the genes. Hence the product and method of utilizing the product inherently do what the applicants invention is intent to accomplish. The burden is on the applicant to show that such is not case.

Liu describes a nucleic acid vaccine and the use of the vaccine to eliminate tumor cells in a mouse model system. Similar to the comments above with respect to the nucleic acid vaccine

of Chen, administering a nucleic acid to a subject is not the same as administering a fusion protein to a subject. Because Liu describes the administration of a nucleic acid vaccine to an animal, and not a fusion protein as is required by claim 1, Liu does not anticipate the claimed method. Furthermore, Liu does not describe using a fusion protein containing an HPV protein antigen of one HPV type to treat a wart caused by an infection with a second HPV type. Accordingly, Liu does not anticipate the claimed invention. Applicants request that the Examiner withdraw the rejection.

CONCLUSIONS

Applicants submit that all grounds for rejection have been overcome, and that all claims are now in condition for allowance, which action is requested.

Attached is a marked-up version of the changes being made by the current amendments. The attached pages are captioned "Version with Markings to Show Changes Made." Also attached are the claims pending in the application upon entry of the above amendments.

Enclosed is a check for $1198 for the three month extension of time and the excess claims fee. Also enclosed is a Transmittal Letter and Petition for Automatic Extension of Time. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 12071-003001.

Respectfully submitted,

Date: April 9, 2003

Jack Brennan
Reg. No. 47,443

Fish & Richardson P.C.
45 Rockefeller Plaza, Suite 2800
New York, New York 10111
Telephone: (212) 765-5070
Facsimile: (212) 258-2291

Version with Markings to Show Changes Made

In the Claims:

Claims 5, 7, and 14-35 have been cancelled without prejudice.

Claims 1, 2, and 4 have been amended as follows:

1. (Amended) A method of treating a wart in a subject, the method comprising administering, to [identifying] a subject who has been identified as [having or suspected of] having a wart,[; and administering to the subject] a composition comprising a fusion protein comprising (1) an Hsp60 protein [a heat shock protein (hsp)] or an immunostimulatory fragment thereof, and (2) [a protein of] a human papilloma virus (HPV) E7 protein[,] or an antigenic fragment thereof, wherein the composition is administered in an amount sufficient to treat the wart, wherein the wart is caused by an infection with a first type of HPV, and wherein the HPV E7 protein or antigenic fragment thereof is of a second type of HPV that differs from the first type of HPV.

2. (Amended) The method of claim 1, wherein the Hsp60 protein [hsp] is a mycobacterial hsp.

4. (Amended) The method of claim 3, wherein the *Mycobacterium bovis* hsp is *Mycobacterium bovis* BCG Hsp65.